# GUIDANCE FOR TESTING

## I. INTRODUCTION

The MMCC has posted a document entitled "Guidance for Testing" as an accompanying document to the previously posted Registration Form for Independent Testing Laboratories (ITLs). This guidance is intended to provide additional detail in support of the requirements of COMAR 10.62.16. This guidance represents the current thinking of the MMCC on the subject of laboratory testing and is intended to provide additional information which will aid the ITLs in the testing of cannabis and cannabis products. This guidance does not establish any rights for a person and is not binding on the MMCC or the public. This guidance will be updated as necessitated by changes in the science and technology in order to continue to reflect current thinking.

## II. SCOPE OF GUIDANCE

The scope of this guidance includes information about testing of both useable cannabis as the final product, medical cannabis finished products, and medical cannabis infused products, as defined in COMAR 10.62.01.

### A. Acronyms

(1) AHPA- American Herbal Pharmacopeia Association.
(2) AHP- American Herbal Pharmacopeia
(3) ANSI/ASQ Z1.4-2008- American National Standards Institute/American Society for Quality
(4) BAM- Bacteriological Analytical Manual
(5) ECD- Electron Capture Detection
(6) EP- European Pharmacopeia

(7) FDA- Food and Drug Administration
(8) FIFRA- Federal Insecticide, Fungicide and Rodenticide Act
(9) GC- Gas Chromatography
(10) GC/ MS- Gas Chromatography/ Mass Spectroscopy
(11) HPLC- High Performance Liquid Chromatography
(12) ICP- Inductively Coupled Plasma
(13) ICP/MS- Inductively Coupled Plasma- Mass Spectroscopy
(14) LC/MS- Liquid Chromatography
(15) ISO Standard- International Standardization Organization
(16) MDA- Maryland Department of Agriculture
(17) OMC- Dutch Office of Medical Cannabis
(18) PPB- parts per billion
(19) SOPs- Standard Operating Procedures
(20) UHPLC- Ultra High Performance Liquid Chromatography
(21) USP-United States Pharmacopeia

## III. ORGANIZATION OF THE GUIDANCE

This guidance is organized into the following sections:

A. Sampling Plan
B. Test Methods and Methods Validation
C. Reference Standards
D. Suggested Acceptance Criteria for Active Components
E. Pesticide Residue Testing- Approaches for consideration
F. Residual Solvent Testing- Approaches for consideration
G. Microbiological Testing and acceptance criteria
H. Heavy Metals
I. Other Tests
J. Stability Testing

## IV. GUIDANCE

### A. SAMPLING PLAN

Sampling is a regulatory requirement as defined in COMAR 10.62.16. The sample for testing should be representative of the batch or lot and be based on appropriate statistical criteria such as ANSI/ASQ Z1.4-2008. This sampling criteria is based on inspection levels, rules and, batch or lot size. The quantity of sample taken from each batch or lot should be of sufficient size to assure the results are representative of

the entire batch or lot. The sample size must also be adequate to perform all the required tests. Sampling should be performed on the entire batch taken from random locations from the top, middle, and bottom ofthe container.

For batch sizes up to 5-10 pounds final yield of useable cannabis, a single composite sample of 8-10 grams (or a quantity sufficient to perform all the required tests) which has been sampled based on the scheme described above, should be acceptable. For batch sizes over 10 pounds but less than 20 pounds final yield, the batch should be divided into two sub-batches and two composite samples be taken for testing according to the sampling scheme described above.

For lots of processed products, sample size should be sufficient to perform all the required tests and should be representative of the entire lot. Sampling should be taken from random locations from the top, middle, and bottom of the container. Since batch sizes will vary based on the finished product dosage form, sub-lotting of larger lot sizes may be required so that the sample size meets appropriate statistical criteria and is representative of the entire lot.

For details about additional sampling requirements, please refer to AHPA draft Recommendations entitled Cannabis Manufacturing, Packaging, Labeling, and Holding Operations, July 2014, section 5.6.

## B. TEST METHODS AND METHODS VALIDATION

All analytical methods for qualitative and quantitative testing are constantly evolving as extraction techniques improve, more sensitive instrumentation is developed, and new tests are required. This guidance attempts to suggest methods which reference the current technologies that are in place today.

All testing methods which are developed in the laboratories should meet or exceed the minimum standard as stated in the American Herbal Pharmacopeia, 2013 Edition. All testing methods must be fully validated to address the accuracy, precision, specificity, linearity, range, and sensitivity of the method.

The cannabinoids which require quantitation, as defined in COMAR 62.15.05, should be tested using a chromatographic method such as HPLC or UHPLC.

The terpenoids should be tested and quantitated using a chromatographic method such as GC or GC-MS, or LC-MS.

Pesticide residue analysis should be performed using LC/MS, GC-MS, or ECD. The sensitivity of the method should be sufficient to quantitate to the lowest detectable and lowest quantitative level as a function of the instrumentation.

Residual solvents (processed products which use organic solvents for extraction), should be quantitated using GC, or GC-MS technology.

Heavy metal analysis should be performed using ICP or ICP-MS technology.

Appropriate methods for performing microbiological testing can be found in FDA's BAM; current edition.

Moisture content analysis should be performed using methodology described in OMC 2014. Alternative methods such as the use of moisture balances may also be acceptable.

### C. REFERENCE STANDARDS

All primary reference standards should be obtained from commercial sources that certify the standards and are accredited to ISO Standard 17025. These standards should be stored according to manufacturer's recommendations and discarded after their expiration dates. Secondary, or "house" standards may be prepared from the primary standards so long as they are prepared and stored according to laboratory SOPs and verified against the primary standard. House standards should only be used within the expiration period as defined in the SOPs.

### D. SUGGESTED ACCEPTANCE CRITERIA FOR ACTIVE COMPONENTS

For active ingredient cannabinoids which are quantitated, and if the label bears the strength of the cannabinoid(s), then the proposed acceptance criteria for usable cannabis as finished product should be between 85% and 115% of the labeled amount. For example, if a label states that the product contains 10mg THC per gram, then an acceptable testing specification would be a range of 8.5-11.5mg THC.

For active ingredients components in processed products which are quantitated and the label bears the strength of the cannabinoid (s), then the proposed acceptance criteria should be between 90% and 110 % of the labeled amount.

For terpenoids which are quantitated, the current edition of the AHP monograph, chapter for terpenoids should be used.

### E. PESTICIDE RESIDUE TESTING- APPROACHES FOR CONSIDERATION

COMAR 62.11.03.G makes reference to pest control as part of growing controls. This guidance suggests three approaches for consideration utilizing best integrated pest management practices, pursuant to Maryland Pesticide Regulations on Labeling Law and the Maryland Pesticide Application Law.

1) Pesticide free production- The entire process from acquisition of seeds or cuttings through harvest would take place under clean, controlled conditions which would be absent of any pesticides, chemical agents, or plant growth regulators.
2) Use of biological pest controls
3) Minimum risk pesticides - exempt from tolerance limits per FIFRA 25 (b). Products must be registered for use in Maryland by an MDA state chemist.

In the case of these three suggested approaches, routine batch to batch release testing of residual pesticides would be required on the first three batches of each product produced.
In order to assure compliance with pesticide use requirements and to validate the allowed approaches in section E, the commission inspection team (or their designee) will periodically inspect and obtain random samples from dispensary and grow facilities. These samples will be tested for the purpose of performing targeted and non-targeted screening as determined by the commission and the MDA. Frequency of inspections could be 6-8 times per year. If testing results reveal compliance with pesticide use requirements, and a pattern of compliance is established, sampling frequency may be reduced.
The list of pesticides which will be monitored represents compounds which have been known to be used by cannabis growers as determined by laboratory testing.
If the testing laboratory detects levels of pesticides residue, then the laboratory will notify the commission of these findings in order for the MMCC compliance staff to take action with the licensed growers.

## F. RESIDUAL SOLVENTS TESTING- APPROACHES FOR CONSIDERATION

1) Carbon Dioxide Gas Extraction- Residual solvent testing on the finished product would not be required as this process does not utilize any solvents in the extraction of the oil from the plant.
2) Non-Solvent Based Extraction- If the process utilizes non-solvent extraction methods, such as heat, steam distillation, ice water, then, residual solvent testing on the finished product would not be required.
3) Solvent Based Extraction- If the process utilizes non-aqueous, hydrocarbon solvents such as butane or propane, the United States Pharmacopoeia (USP) chapter 467 for residual solvents recommends concentration limits and testing procedures for these and other solvents which may be used in extraction processes.

## G. MICROBIOLOGICAL TESTING AND ACCEPTANCE CRITERIA

For microbiological impurities which include those defined in COMAR 10.62.15.0005B(3)(a)-(g), the current edition of the American Herbal Pharmacopeia(AHP), Cannabis Inflorescence monograph, Microbial and Fungal Limits chapter should be incorporated for acceptable limits and test procedures.

## H. HEAVY METALS

Heavy metals as defined in COMAR 10.62.15.05B(1) include mercury, cadmium, lead, and arsenic. The USP chapters 232 for limits and 233 for testing procedures may be used, as well as the AHP monograph Metal Limits chapter.

## I. OTHER TESTS

Other tests which are defined in COMAR 10.62.15.05B(4) include odor, appearance, fineness, and moisture content. The AHP chapter defined as Limit Tests includes reference to these tests. The chapter

cross references the European Pharmacopeia (EP), the USP, as well as the Dutch Office of Medical Cannabis (OMC). All three of these sources include details about sample preparation and acceptance limits which may be used for quality control release testing.

## J. STABILITY TESTING

COMAR 10.62.15.07 requires that licensed growers and licensed processors provide a sample for stability testing at six month intervals sufficient to ensure product potency, purity, and to provide support for the product expiration date. The stability testing sample should be taken from the reserved sample of the batch. The stability testing sample should be submitted to the independent testing lab at the 6 and 12 month intervals post batch release, or at 6 month intervals through the intended expiration period (if the expiration dating exceeds 12 months). Tests which typically are performed on stability samples should include the cannabinoids and terpenes, microbiological testing, and moisture content.

At this time, there is limited data which has been published about the long term stability of useable cannabis products and processed cannabis products. Adequacy of the container/closure systems to maintain stability of these products over the intended shelf life needs to be established.

Accordingly, at this time, stability testing results may be reported on a "read and record" basis in order to compile a base of date which will be used in the future to establish actual stability specifications.